1646

AF/1646

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND PATENT INTERFERENCES

In re Application of:	)	
	)	
Billger *et al.*	)	
	)	
Serial No.: 09/674,002	)	Group Art Unit: 1646
	)	
Filed: December 27, 2000	)	Examiner: Ruixiang Li
	)	
For: PROTEIN FORMULATIONS	)	

Mail Stop Appeal Brief - Patents
Washington, D.C. 20231

BRIEF ON APPEAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND PATENT INTERFERENCES

In re Application of:	)	
	)	
Billger *et al.*	)	
	)	
Serial No.: 09/674,002	)	Group Art Unit: 1646
	)	
Filed: December 27, 2000	)	Examiner: Ruixiang Li
	)	
For: PROTEIN FORMULATIONS	)	

Mail Stop Appeal Brief - Patents
Washington, D.C. 20231

Sir:

BRIEF ON APPEAL
UNDER 37 C.F.R. § 1.191

This Appeal Brief is filed in triplicate, together with a check in the amount of $320.00 covering the appeal fee. If this fee is deemed insufficient, Appellants authorize charging any deficiency (as well as crediting any balance) to deposit account 19-0741.

This is an appeal from the Office Action dated March 24, 2003, and the Advisory Action dated July 15, 2003, finally rejecting claims 1-7, 9, 12, 17, 18, 29-28, and 31-36 under 35 U.S.C. § 103(a) over Holthuis *et al.*, U.S. patent No. 5,496,801, in view of Endo *et al.*, U.S. patent No. 5,563,122.

CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, NPS Allelix Corporation, 6850 Goreway Drive, Mississauga, Ontario, Canada.

II. RELATED APPEALS AND INTERFERENCES

None of the Appellants, Appellants' legal representative, or their assignee is aware of any related appeals or interferences that will affect directly or be affected directly by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1-7, 9, 12, 17, 18, 20-28, and 31-36, set forth in the Advisory Action dated July 15, 2003, are on appeal and are reproduced in an APPENDIX to this brief.

IV. STATUS OF AMENDMENTS

In response to a final Office Action dated March 24, 2003, an Amendment of June 20, 2003, effected a revision of claims 1-7, 9, 12, and 24 and the cancellation of claims 8, 10, 11, and 19. An Advisory Action dated July 15, 2003, indicated the June 20th Amendment would be entered for the purposes of appeal.

V. SUMMARY OF INVENTION

The present invention concerns a highly concentrated human parathyroid hormone formulation that is useful for the treatment of, or the prevention of, bone disorders such as osteoporosis. As a highly concentrated source of parathyroid hormone, the present composition is particularly useful as a liquid multidose formulation from which daily unit doses can be administered by the end-user. For this purpose, the parathyroid hormone present in such a formulation must remain stable as a liquid for many days. This is achieved when the formulated parathyroid hormone includes the claimed combination of (i) highly concentrated human parathyroid hormone, (ii) sodium chloride, (iii) mannitol, (iv) a preservative, and (v) a buffer of pH 4 to 6. Specification at page 5, lines 13-31.

A. ISSUES

A. The Examiner maintained a rejection of claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 under 35 U.S.C. § 103(a).

B. Independent claims 1, 9, and 24, were amended to incorporate from original claim 10, the recitation of "liquid," but still were deemed obvious over Holthuis *et al.* in view of Endo *et al.*

C. The Examiner found the cited references supportive of the rejection because they teach a stable pharmaceutical formulation in both liquid form and lyophilized form that is comprised of human parathyroid hormone (1-84), mannitol as excipient, and citrate as buffering agent.

VI. COURSE OF PROSECUTION

For the record, Appellants note that they did not receive a first action on the merits until 21 months after the filing date of this application and only then after they had tendered two status inquiries to the USPTO.

Appellants also note that the application has passed through the hands of two examiners. The first examiner, Eliane Lazar-Wesley, rejected the claims over the Holthuis/Endo combination. Office Action dated September 10, 2002, at page 5. When prosecution was taken up by the second examiner, Ruixian Li, Appellants had presented evidence to establish the absence of motivation (indeed, a teaching away) in the art vis-à-vis the proposed modification of Holthuis in view of Endo. Examiner Ruixiang Li maintained the prior rejection, however, without substantive comment on the proffered evidence.

VII. GROUPING OF CLAIMS

Claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 stand and fall together.

VIII. SUMMARY OF THE ARGUMENT

The Examiner has not established a *prima facie* case of obviousness, because neither of the cited references suggests incorporating sodium chloride (Endo *et al*) with parathyroid hormone (Holthuis *et al*), where the parathyroid hormone is highly concentrated and in liquid form, as presently claimed. In fact, to have done so would have contravened conventional wisdom. The conventional wisdom held that sodium chloride would cause dimers in parathyroid hormone formulations and that highly concentrated proteins, including parathyroid hormone, precipitate from solutions that contain sodium chloride. Conventional wisdom also predicted that a liquid-formulated parathyroid hormone would destabilize during storage, and degrade to produce undesirable injection material. It was totally unexpected, therefore, that Appellants' liquid composition, containing both chloride ion and highly concentrated parathyroid hormone, lacked the undesirable traits predicted by the conventional wisdom.

It should further be appreciated that the cited prior art is not concerned with the stability of parathyroid hormone in liquid. Holthuis *et al.* describes the effect of long term storage on the stability of freeze-dried parathyroid hormone and says nothing on the stability of a highly concentrated liquid formulation that contains sodium chloride. Similarly, Endo *et al.* teach the injection of the total volume of a unit dose formulation of parathyroid hormone, which is injected by the end-user once the parathyroid hormone powder has been reconstituted with a liquid vehicle. For this reason, Endo *et al.* is unconcerned with the post-reconstituted stability properties of that parathyroid hormone preparation, since there is none of the reconstituted, liquid parathyroid hormone remains after injection.

The prior art thus does not teach, suggest or motivate the preparation of liquid formulations that incorporate both highly concentrated parathyroid hormone and chloride ion. Indeed, the prior art teaches that such a combination is to be avoided. Accordingly, the pending obviousness rejection is improper and should be reversed.

IX. ARGUMENT

To establish a *prima facie* case of obviousness under Section 103(a), the Examiner must show (1) at least a suggestion in the prior art of each element recited in the claim at issue, (2) some suggestion or motivation to have combined those elements, as proposed by the examiner, and (3) a reasonable expectation of success, likewise evidenced in the prior art, for the proposed combination. Furthermore, the Examiner must ascertain that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made.

As Appellants have demonstrated on the record, however, the cited art in the present case does not suggest or evidence motivation for the inclusion of sodium chloride in a solution of highly concentrated parathyroid hormone, as is presently claimed; and the subject matter ***as a whole*** therefore is not obvious. Moreover, the Examiner did not consider the totality of the evidence in maintaining the obviousness rejection; indeed, the evidence of record teaches against the inclusion of sodium chloride in a liquid parathyroid hormone formulation.

A. <u>There Is No *Prima Facie* Case Of Obviousness: The Prior Art Provides No Motivation To Incorporate Sodium Chloride (Endo) In A Highly Concentrated Parathyroid Hormone Preparation (Holthuis) That Is In Liquid Form</u>

(i) <u>The Nature of the Obviousness Rejection</u>

Examiner Lazar-Wesley rejected original claims 8 and 9 under Section 103(a) as unpatentable over Holthuis in view of Endo alleging that "it would have been obvious for one of skill in the art at the time of the invention, to modify the preparation of Holthuis, by adding a sodium chloride *solution* as taught by Endo, because Endo teaches that a combination of sodium chloride and sugar achieves a higher stability for a [parathyroid hormone] preparation." Office Action dated September 10, 2002, at page 6 (emphasis added).

Examiner Li upheld this rationale and further rejected claims 1-7, 10-12, 17-18, 21-23, 26-28, and 31-36, alleging that it would have been obvious "to include sodium chloride in the formulation of Holthuis *et al.* with a reasonable expectation of success."

Office Action dated March 24, 2003, at page 5. Examiner Li concluded that "one would have been motivated to do so because Endo *et al.* demonstrate that addition of sodium chloride, in addition to mannitol, further stabilizes" parathyroid hormone. *Id.* at pages 5 and 6.

(ii) There Is No Teaching In The Prior Art Of A Stable ***Liquid*** Parathyroid Hormone

Both Examiners have misunderstood the cited prior art: Endo added sodium chloride and mannitol to produce stable formulated parathyroid hormone (consisting of residues 1-34) in the freeze-dried state. The presently claimed invention, however, is directed to a *liquid* parathyroid hormone formulation that contains sodium chloride. The present invention discovered that, unexpectedly, a solution of parathyroid hormone can be stored for months without destroying the integrity of that protein, even though the solution contains sodium chloride.

Lyophilized and liquid preparations of parathyroid hormone are not fungible, as evidenced by conventional wisdom which explicitly taught away from adding sodium chloride to liquid parathyroid hormone (see Section B below). Thus, Endo reported that "improved stability for *lyophilized* preparations of PTH can be obtained by combining a constant amount of sodium chloride with a sugar," column 1, lines 30-33 (emphasis added).

Holthuis similarly adhered to prior-art concepts. Neither Endo nor Holthuis suggested using sodium chloride in a liquid formulation of parathyroid hormone, and neither publication provided any reason or motivation for the skilled artisan to have made this modification, especially in light of the contrary teachings of the art, discussed below. Accordingly, there is no suggestion from Holthuis or Endo to generalize from a lyophilized to a liquefied parathyroid hormone formulation that can be stored for months at a time, and nothing in the prior art predicted or suggested Appellants' unexpected results.

Indeed, Holthuis was not concerned with, and did not address, the stability of a liquid parathyroid hormone that contained sodium chloride. The main thrust of Holthuis was to establish that a freeze-dried parathyroid preparation was stable over a period of time. The stability of Holthuis' freeze-dried preparations after "1, 2, 3, 6 and 9 months" of storage was

analyzed by reconstituting the dried preparation with water, allowing up to one minute for reconstitution and then removing the solution for analysis. See Holthuis column 6, lines 50-58. Accordingly, such a parathyroid liquid was only available temporarily and was only used analytically to determine the integrity of the stored *powder*.

(iii) The skilled artisan would not have been motivated to depart from the teachings of Holthuis and Endo in order to incorporate sodium chloride in a liquid formulation of parathyroid hormone

Informed by Endo, the skilled artisan might have been motivated to add sodium chloride and sugar to Holthuis' freeze-dried parathyroid hormone. To have arrived at Appellants' claimed invention, however, the skilled artisan would have had to have departed from the "lyophilized storage" teachings of both Holthuis and Endo. That is, the person of ordinary skill (1) would have to have been prompted to add sodium chloride and sugar to Holthuis' parathyroid hormone and (2) would have had to have been motivated to retain and store that mixture in liquid form. Clearly, the driving force or rationale to have made such modifications to Holthuis are absent from the art of record.

By contrast, the present invention is to a solution of highly concentrated parathyroid hormone that could be stored for months without any appreciable degradation or reduction in stability, *even though the liquid contained sodium chloride*.

B. **Incorporating Sodium Chloride In A Highly Concentrated Liquid Parathyroid Hormone Formulation Would Have Contravened Conventional Wisdom As Noted In Holthuis**

Prior to Appellants' invention, it was well established that the presence of sodium chloride in such a liquid can cause precipitation of highly concentrated proteins. Indeed, the "salting out" procedure is a standard method for precipitating proteins from aqueous solutions, especially as part of a purification process. The conventional wisdom, as evidenced in the cited art, taught away from creating a highly concentrated parathyroid hormone liquid that contained sodium chloride.

(i) Holthuis references "Martindale: The Extra Pharmacopeia," which teaches away from incorporating parathyroid hormone in a sodium chloride solution

During prosecution Appellants pointed out that the prior art explicitly taught away from adding sodium chloride to liquid parathyroid hormone and, hence, that the obviousness rejection was untenable. To further support of this point, Appellants submitted to the Patent Office page 1338 of the MARTINDALE: THE EXTRA PHARMACOPEIA, The Pharmaceutical Press, London, 29th Edition, 1989 (of record). That publication states that "solutions of parathyroid hormone may be diluted with glucose 2.5 to 5%. Sodium chloride solutions **should not be used as they often cause precipitation**" (second full paragraph under the Entry 8051-x, entitled "Parathyroid Hormone") (emphasis added).

In column 1, at lines 62-64, Holthuis cites *this same Martindale reference*, in the portion of the specification that describes various formulations of parathyroid hormone. Thus, Holthuis was well aware of the detrimental effects of sodium chloride in a solution of parathyroid hormone and, by reference, informs the skilled artisan of such effects. It is not surprising, then, that Holthuis does not contemplate the use of a sodium chloride solution in formulating parathyroid hormone.

(ii) The prior art, as evidenced by CA 2,234,724, demonstrated that sodium chloride, even in lyophilized preparations, causes undesirable dimerization of parathyroid hormone

Similarly, Canadian patent application, CA 2,234,724 (of record) taught that a mixture of sodium chloride and parathyroid hormone was undesirable. The '724 application indicated that, even in lyophilized preparations, sodium chloride "favours the formation of dimers," which are "problematic in pharmaceutical forms of administration since they can lead to undesired side-effects when administered to patients due to immunological reactions" (paragraph bridging pages 1 and 2). Furthermore, the '724 reference states at page 2 that such dimerization can lead to "a loss of activity . . . especially when stored over a long time period." Accordingly, the '724 reference concluded that the "pharmaceutical forms of administration" of parathyroid hormone "are preferably essentially free of chloride ions since chloride ions favour the formation of dimers."

The applicants of the '724 case demonstrated experimentally that lyophilized parathyroid hormone made with sodium chloride "favours the formation of dimers and shows a lower PTH content after a storage period of one or three months," and can therefore "be ranked as [a] less suitable pharmaceutical form of administration in relation to storage stability." They concluded that "in principle it has turned out that the ***addition of chloride ions has a negative effect on the storage stability***" (paragraph bridging pages 10 and 11; emphasis added).

(iii) With respect to added sodium chloride, the skilled artisan would not have been motivated to modify parathyroid hormone-containing compositions in the prior art, as posited by the Examiner

In view of Endo and Holthuis, and informed by the art exemplified by Martindale and the '724 application, it is apparent that the skilled artisan would not have been inclined (indeed, would have been opposed to) the incorporation of sodium chloride into a reconstituted, liquid solution, per Holthius. The skilled artisan also would have had no expectation that such a modification would result in a successful product since the art taught that chloride ions precipitate parathyroid hormone from solution and cause the formation of dimers in lyophilized parathyroid hormone.

C. **The Examiner Failed To Base The Ultimate Determination Of Patentability On The *Entire* Record, By A Preponderance Of Evidence, With Due Consideration To The Persuasiveness Of Any Arguments And Any Secondary Evidence**

According to U.S. Patent Office practice, an examiner must consider any evidence supporting patentability, whether that evidence is found in the specification or is submitted by the applicant. Thus, a decision to maintain a rejection must itself be grounded on the totality of the evidence.

In responding to Appellants' paper dated January 10, 2003, in which Appellants bolstered their support of patentability based on the '724 patent, the Examiner effectively dismissed that evidence by stating that, "while the Canadian patient [sic] CA 2,234,724 may teach a formulation preferably free of chloride ions, **the majority of the art** teach the use of

saline . . . as a water-based vehicle" (emphasis added). Yet the Examiner cited no other reference except for Holthuis, already of record, to support his position regarding "the majority" indication in the art.

Furthermore, even though Appellants provided the Examiner with a copy of the Martindale reference in response to the final Office Action, the Examiner appears to have dismissed entirely the teachings of Martindale. The Advisory Action of July 15, 2003, is silent on the impact of Martindale, which is in direct opposition to the Examiner's rationale for rejecting the claims over Holthuis in view of Endo. Accordingly, it does not appear to be the case that the Examiner considered the *totality of the evidence* in maintaining the obviousness rejection and, thus, the Examiner has not established a *prima facie* case of obviousness.

* * * *

Because the cited references do not teach or suggest, either alone or in combination the claimed invention, it is courteously requested that the Board reverse the Examiner's rejections of the claims.

X. CONCLUSION

The Board is respectfully requested to reconsider and reverse the outstanding rejections.

Respectfully submitted,

Date: 24 September 2003

By: S. A. Bent

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

CLAIMS ON APPEAL

1. (Previously amended) A stable, liquid pharmaceutical formulation of human parathyroid hormone at a concentration of 0.3 mg/ml to 10 mg/ml, comprising (i) human parathyroid hormone, (ii) a pharmaceutically acceptable buffer of pH 4 to 6, (iii) NaCl, (iv) mannitol, (v) a preservative, and (vi) water.

2. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the human parathyroid hormone is human recombinant parathyroid hormone.

3. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the human parathyroid hormone is a full-length parathyroid hormone.

4. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the concentration of the human parathyroid hormone is from 0.3 mg/ml to 5 mg/ml.

5. (Previously amended) The pharmaceutical formulation according to claim 4, wherein the concentration of the human parathyroid hormone is from 1 mg/ml to 3 mg/ml.

6. (Previously presented) The pharmaceutical formulation according to claim 1, wherein the pharmaceutically acceptable buffer is a citrate buffer at a concentration from 5 to 20 mM.

7. (Previously presented) The pharmaceutical formulation according to claim 1, wherein the pharmaceutically acceptable buffer has a pH between 5 and 6.

9. (Previously presented) A stable, liquid pharmaceutical formulation of human parathyroid hormone, comprising 1 to 3 mg/ml parathyroid hormone, 2 to 5 mg/ml

NaCl, 20 to 50 mg/ml mannitol, a preservative, and 5 to 10 mM citrate buffer at a pH between 4 and 6.

12. (Previously presented) A process for the preparation of a pharmaceutical formulation according to claim 1, comprising dissolving human parathyroid hormone, to a concentration from 0.3 to 10 mg/ml, sodium chloride, and mannitol in a pharmaceutically acceptable buffer having a pH between 4 and 6.

17. (Previously presented) A method for treating a bone related disorder or reducing or inhibiting bone loss associated with a bone related disorder, comprising administering to a mammal, including man, in need of such treatment or inhibition, an effective amount of the formulation of claim 1.

18. (Previously presented) The method according to claim 17, wherein the bone related disorder is osteoporosis.

20. (Previously added) The pharmaceutical formulation of claim 9, wherein the preservative is benzyl alcohol, m-cresol or EDTA.

21. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human recombinant parathyroid hormone.

22. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human full-length parathyroid hormone.

23. (Previously added) The pharmaceutical formulation of claim 9, wherein the pH of the citrate buffer is between 5 and 6.

24. (Previously presented) A stable, liquid pharmaceutical formulation comprising 1 to 3 mg/ml parathyroid hormone, 2 to 5 mg/ml NaCl, 20 to 50 mg/ml mannitol, 5 to 10 mM citrate buffer at a pH between 4 and 6, and a preservative.

25. (Previously added) The pharmaceutical formulation of claim 24, wherein the preservative is benzyl alcohol, m-cresol or EDTA.

26. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human recombinant parathyroid hormone.

27. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human full-length parathyroid hormone.

28. (Previously added) The pharmaceutical formulation of claim 24, wherein the pH of the citrate buffer is between 5 and 6.

31. (Previously added) The pharmaceutical formulation of claim 1, wherein the concentration of the NaCl is between 2 to 5 mg/ml.

32. (Previously added) The pharmaceutical formulation of claim 1, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

33. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

34. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

35. (Previously added) A method for treating a bone related disorder or reducing or inhibiting bone loss associated with a bone related disorder, comprising administering to a mammal, including man, in need of such treatment or inhibition, an effective amount of the formulation of claim 9.

36. (Previously added) The method according to claim 35, wherein the bone related disorder is osteoporosis.